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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/285,429	04/02/1999	BRET A. SHIRLEY	5784-9	3707

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EXAMINER

KAM, CHIH MIN

ART UNIT PAPER NUMBER

1653

DATE MAILED: 03/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary

Application No.

09/285,429

Applicant(s)

SHIRLEY ET AL.

Examiner

Chih-Min Kam

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 January 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 21-34, 45 and 46 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 21-34 and 45-46 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of the Claims

1. Claims 21-34 and 45-46 are pending.

Applicants' response filed January 6, 2005 is acknowledged, and the response has been fully considered. Claim 21-34 and 45-46 are examined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

2. Claims 21-34 and 45-46 remain rejected under 35 U.S.C. 103(a) as being unpatentable over by Clark *et al.* (U. S. Patent 5,597,802, published January 28, 1997).

Clark *et al.* teach a composition comprising IGF-I, an osmolyte, a stabilizer and a buffer solution of about pH 5-5.5, and a formulation comprising mixing the IGF-I composition with a

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buffered solution comprising GH at pH 6.0, where the buffer may be any suitable buffer that is GRAS (generally regarded as safe) and confers a pH of 5-6 on the GH+IGF-I formulation and a pH of about 5-5.5 on the IGF-I formulation, and the buffers include acetate, succinate, phosphate, and citrate buffers (column 13, lines 16-24). The reference indicates a particular composition may comprise IGF-I and GH in a weight ratio of IGF-I: GH of between 2:1 and 100:1, 0.05-0.3 mM of osmolyte (e.g., sodium chloride, potassium chloride and mannitol), about 0.1-0.6 mg/ml of at least one stabilizer, about 1-5 mg/ml of a surfactant and about 5 to 100 mM of a buffer at pH 5-6 (column 12, lines 14-35; claims 21-30). The reference also suggests that the composition may be administered parenterally, preferably by injection, and the formulation is sterile (column 5, lines 44-52; column 9, line 57-column 10, line 10; column 13, lines 38-41; claim 45), wherein IGF-I can be a recombinant human IGF-I (column 8, lines 46-50; claim 31); and the composition may contain 2-50 mg/ml of sodium chloride (corresponding to 34-855 mM) as osmolyte (also referred as isotonic modifier; column 12, lines 26-35; column 14, lines 12-23; claim 32 and 46). The reference also teaches the final preparation can be a stable liquid or lyophilized solid (column 13, lines 33-37; claims 33 and 34). Although the reference does not specifically disclose an example of succinate buffer at a concentration of 10-40 mM, the reference does suggest the use of a suitable buffer such as succinate from a group of acetate, succinate, phosphate and citrate buffers in preparing a composition comprising IGF-I at pH 5-6, where a concentration of 5 to 100 mM buffer can be used, and it is known that succinate having pK₂ of 5.64 is used to prepare a buffer in the pH range of 5.5-6.5, thus at the time of invention was made, it would have been obvious that one of ordinary skill in the art is motivated to prepare a pharmaceutical composition comprising IGF-I at pH 6 using the succinate buffer as suggested by

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the reference, which results in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

In response, applicants indicate that the '802 patent does not recite any concentration limitation for a succinate buffer, it only mentions succinate buffer in two passages (see column 11, lines 41-58; column 13, lines 16-24); the Examiner solely derives the motivation or desirability of using succinate buffer from the fact that the '802 patent recites succinate buffer in a generic Markush group, and the inclusion of an element in a Markush group does not render an invention Prima facie obvious absent any other specific rationale or desirability of using the recited element; to the extent that the Examiner is implicitly asserting that succinate is an "equivalent" buffer to those used in the actual IGF-I or IGF-I + GH formulations disclosed by the '802 patent, Applicants assert that the experimental data presented in this cited patent demonstrate that buffers used in such compositions are not equivalent. Specifically, Figures 13 through 24 of the '802 patent demonstrate that the biological effects of these formulations can vary significantly depending upon the buffer; furthermore, the statement in the cited patent indicates the desirability of formulating IGF-I or IGF-I + GH with acetate buffers (see arguments presented on pages 3-4 of Applicants' response filed July 12, 2004; pages 2-5 of the response filed January 6, 2005).

Applicants' response has been considered, however, the argument is not found persuasive because the '802 patent does suggest the use of succinate from a group of buffers containing a limited members (i.e., acetate, succinate, phosphate, and citrate) and the use of a concentration of 5 to 100 mM of buffer for preparing a pharmaceutical composition comprising IGF-I at pH 5-6, and it is known that succinate with pK₂ of 5.64 is suitable for preparing a buffer in the pH range

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of 5.5-6.5 and with $pK_1 = 4.21$ is also suitable for preparing a buffer of pH 3.2-5.2. Although the reference cites IGF-I compositions are preferably formulated with sodium acetate buffer, it is obvious that acetate having pK_a of 4.76 is preferred for a buffer of pH 3.6-5.6, but it is not suitable for a buffer at pH 6.0. Furthermore, the preferable embodiment (i.e., acetate buffer) does not exclude other embodiments (i.e., succinate, citrate) in the genus. Regarding the issue that buffers used in such compositions are not equivalent, e.g., the biological effects of these formulations can vary significantly depending upon the buffer, which again does not exclude the use of succinate as a buffer for a pharmaceutical composition at pH 5.5-6.0. Therefore, it is obvious that one of ordinary skill in the art would prepare a pharmaceutical composition comprising IGF-I at pH 5.0-6.0 using the succinate buffer at a concentration of 5 to 100 mM as suggested by the reference and the known pK_a of succinate, which results in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

Conclusion

3. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

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however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

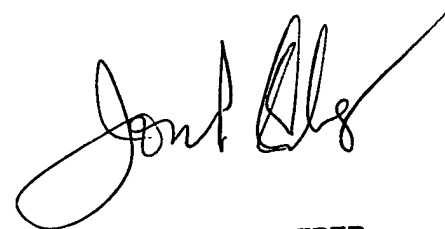
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached at 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-272-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D. *CMK*
Patent Examiner

CMK

March 1, 2005



JON WEBER
SUPERVISORY PATENT EXAMINER